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(71) Applicant *(for all designated States except US)*: GLAXOSMITHKLINE BIOLOGICALS SA [BE/BE]; Rue de l'Institut 89, B-1330 Rixensart (BE).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: BIEMANS, Ralph [BE/BE]; GlaxoSmithKline Biologicals S.A., Rue de l'Institut 89, B-1330 Rixensart (BE). DENOEL, Philippe [BE/BE]; GlaxoSmithKline Biologicals S.A., Rue de l'Institut 89, B-1330 Rixensart (BE). FERON, Christiane [BE/BE]; GlaxoSmithKline Biologicals S.A., Rue de l'Institut 89, B-1330 Rixensart (BE). GORAJ, Karine [BE/BE]; GlaxoSmithKline Biologicals S.A., Rue de l'Institut 89, B-1330 Rixensart (BE). POOLMAN, Jan [NL/BE]; GlaxoSmithKline Biologicals S.A., Rue de l'Institut 89, B-1330 Rixensart (BE). WEYNANTS, Vincent [BE/BE]; GlaxoSmithKline Biologicals S.A., Rue de l'Institut 89, B-1330 Rixensart (BE).

(74) Agent: LUBIENSKI, Michael, John; GlaxoSmithKline, CIP (CN925.1), 980 Great West Road, Brentford, Middlesex TW8 9GS (GB).

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Published:
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— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments*

(88) Date of publication of the international search report: 22 July 2004

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: VACCINE COMPOSITIONS COMPRISING L2 AND/OR L3 IMMUNOTYPE LIPOOLIGOSACCHARIDES FROM LGTB- NEISSERIA MINIGITIDIS

(57) Abstract: The present invention relates to the field of neisserial vaccine compositions, their manufacture, and the use of such compositions in medicine. More particularly it relates to processes of making novel engineered meningococcal strains which are more suitable for the production of neisserial, in particular meningococcal, outer-membrane vesicle (or bleb) vaccines. Advantageous processes and vaccine products are also described based on the use of novel LOS subunit or meningococcal outer-membrane vesicle (or bleb) vaccines which have been rendered safer and/or more effective for use in human subjects. In particular combinations of gene downregulations are described such as PorA & OpA, PorA and OpC, OpA and OpC, and PorA and OpA and OpC. Alternatively, or in addition, lgtB$^-$ is shown to be an optimal mutation for effectively and safely using L3 and/or L2 LOS in Neisseria vaccine compositions. Bleb vaccines derived from lgtB$^-$ and capsular polysaccharide deficient meningococcal mutants are further described; as are advantageous methods of making bleb preparations where LOS is to be retained as an important antigen.

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INTERNATIONAL SEARCH REPORT

Int[redacted] Application No
PCT/EP 03/08568

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K39/095 C12N1/21 A61P37/04 A61K39/102

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, BIOSIS, EMBASE, PAJ, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	JENNINGS M P ET AL: "Molecular analysis of a locus for the biosynthesis and phase-variable expression of the lacto-N-neotetraose terminal lipopolysaccharide structure in Neisseria meningitidis." MOLECULAR MICROBIOLOGY. ENGLAND NOV 1995, vol. 18, no. 4, November 1995 (1995-11), pages 729-740, XP002270109 ISSN: 0950-382X	11
Y	page 731, column 1, paragraph 2 -column 2 page 733, column 1, paragraph 2 -page 734, column 1, paragraph 2 page 737, column 1, last paragraph -column 2	1-8, 12-14, 16-20, 35,48

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

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"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

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"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
7 May 2004	18.05.2004

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Noë, V

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 01/09350 A (DALEMANS WILFRIED L J ;SMITHKLINE BEECHAM BIOLOG (BE); THIRY GEORG) 8 February 2001 (2001-02-08) cited in the application abstract page 2, line 1 - line 22 page 17, line 12 - line 25 page 20, line 11 - line 22 page 23, line 21 -page 24, line 9 page 31, line 1 - line 22 page 33, line 1 - line 30 page 36, line 5 - line 28 example 8	1-8, 16-20, 36,39, 40,42, 43,45, 47,49
Y	VERHEUL A F M ET AL: "PREPARATION, CHARACTERIZATION, AND IMMUNOGENICITY OF MENINGOCOCCAL IMMUNOTYPE L2 AND L3,7,9 PHOSPHOETHANOLAMINE GROUP-CONTAINING OLIGOSACCHARIDE-PROTEIN CONJUGATES" INFECTION AND IMMUNITY, AMERICAN SOCIETY FOR MICROBIOLOGY. WASHINGTON, US, vol. 59, no. 3, 1 March 1991 (1991-03-01), pages 843-851, XP002032436 ISSN: 0019-9567 abstract page 844, column 1, paragraph 2 -page 845, column 1, paragraph 1 page 845, column 1, paragraph 3 page 847, column 1, paragraph 2 -column 1, last paragraph	12,14
Y	GAO LIHUI HU XUJING ET AL: "Study on the LOS antigenicity of 2 candidate strains for meningococcal vaccine of serogroup B" BIOSIS, XP002133714 abstract	12
X	WAKARCHUK W ET AL: "Functional relationships of the genetic locus encoding the glycosyltransferase enzymes involved in expression of the lacto-N-neotetraose terminal lipopolysaccharide structure in Neisseria meningitidis" JOURNAL OF BIOLOGICAL CHEMISTRY, AMERICAN SOCIETY OF BIOLOGICAL CHEMISTS, BALTIMORE, MD, US, vol. 271, no. 32, 9 August 1996 (1996-08-09), pages 19166-19173, XP002084666 ISSN: 0021-9258 abstract	11

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 94/08021 A (LEY PETER ANDRE V D ;NEDERLANDEN STAAT (NL); POOLMAN JAN THEUNIS () 14 April 1994 (1994-04-14) cited in the application	21, 24-28, 33,34, 37,38, 40,46, 50,51
Y	abstract page 5, line 13 -page 6, line 16 page 6, line 31 -page 7, line 8 page 9, line 16 - line 35 page 15, line 13 - line 35 page 16, line 11 - line 22 page 17	35,36, 39,43, 47-49
X	QUAKYI EMMANUEL K ET AL: "Modulation of the biological activities of meningococcal endotoxins by association with outer membrane proteins is not inevitably linked to toxicity" INFECTION AND IMMUNITY, vol. 65, no. 5, 1997, pages 1972-1979, XP001184760 ISSN: 0019-9567 abstract page 1972, column 2, last paragraph -page 1973, column 2, paragraph 1 page 1974, column 2, last paragraph -page 1978, column 1, paragraph 1 page 1978, column 1, paragraph 4 page 1978, column 2, last paragraph	1-3,11, 12,16,19
X	GU X X ET AL: "Preparation, characterization, and immunogenicity of meningococcal lipooligosaccharide-derived oligosaccharide-protein conjugates" INFECTION AND IMMUNITY, AMERICAN SOCIETY FOR MICROBIOLOGY. WASHINGTON, US, vol. 61, no. 5, May 1993 (1993-05), pages 1873-1880, XP002102900 ISSN: 0019-9567 abstract page 1873, column 2, paragraph 1 - paragraph 2 page 1876, column 2, paragraph 2 -page 1878, column 2, paragraph 3 page 1878, column 2, last paragraph -page 1879, column 1, paragraph 1	12,14, 16,17

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	ZAKIROV M M ET AL: "Immunological activity of Neisseria meningitidis lipooligosaccharide incorporated into liposomes" ZHURNAL MIKROBIOLOGII EPIDEMIOLOGII I IMMUNOBIOLOGII, vol. 0, no. 1, 1995, pages 49-53, XP008027121 ISSN: 0372-9311 abstract	12,13,16
Y	EP 0 941 738 A (AMERICAN CYANAMID CO) 15 September 1999 (1999-09-15) cited in the application	40,42, 43,45,48
A	paragraphs '0013!,'0014!,'0016!,'0029!,'0030!,'0034!-'0038!; claims 1,4-7,13	21-36
P,X	US 6 531 131 B1 (GU XIN-XING ET AL) 11 March 2003 (2003-03-11) abstract column 2, line 33 -column 3, line 1 column 3, line 18 - line 22 column 5, line 20 - line 43	12,14, 16,17

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP 03/08568

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☒ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
see FURTHER INFORMATION sheet PCT/ISA/210

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☒ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
1-8,11-31,37-39 (partially), 32-36, 40-52 (completely)

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☒ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. Claims: 1-8,11-20 (partially)

LgtB- Neisserial strain with an L2 LOS or L3 LOS immunotype; neisserial bleb preparation derived therefrom; neisserial bleb preparation comprising a combination of blebs derived from Neisserial strains with an L2 LOS immunotype or an L3 immunotype wherein at least one strain is lgtB-; LOS preparation isolated from lgtB- neisserial strain comprising immunotype L2 and/or L3 LOS; immunogenic composition or vaccine comprising said neisserial bleb preparation or LOS preparation and process of manufacturing said vaccine.

2. Claims: 1-8,11-20 (partially)

Neisserial strain with an L2 LOS or L3 LOS immunotype; neisserial bleb preparation comprising a combination of blebs derived from a Neisserial strain with an L2 LOS immunotype and a neisserial strain with a L3 LOS immunotype; LOS preparation isolated from said neisserial strain comprising immunotype L2 and/or L3 LOS; immunogenic composition or vaccine comprising said neisserial bleb preparation or LOS preparation and process of manufacturing said vaccine.

3. Claims: 9-20 (partially)

Neisserial strain having 2 or more of the following outer membrane molecules downregulated, PorA, PorB, OpA, OpC, PilC or FrpB; Neisserial bleb preparation derived from said neisserial strain; LOS preparation isolated from said neisserial strain; immunogenic composition or vaccine comprising said neisserial bleb preparation or LOS preparation and a process of manufacturing said vaccine.

4. Claims: 21-52

Bleb preparation from a gram-negative bacterial strain with an outer-membrane protein conjugated to LOS integrated in its outer membrane; immunogenic composition or vaccine comprising said bleb preparation; process of producing said bleb preparation.

Continuation of Box I.2

Present claims 21-31,37-39 relate to an extremely large number of possible bleb preparations, namely derived from Gram negative bacterial strains. Support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT is to be found, however, for only a very small proportion of the bleb preparations claimed. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Consequently, the search has been carried out for those parts of the claims which appear to be supported and disclosed, namely those parts relating to the bleb preparations from Moraxella catarrhalis, a non-typeable haemophilus influenzae strain and from Neisserial strains (see description page 13, line 6-11 and examples).

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

Inter[illegible] Application No
PCT/EP 03/08568

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